both EPO treatment groups exhibited attenuation of LV dilatation and improved LV systolic function after MI, the EPO-L group exhibited a trend towards smaller LVDd and LVDs, lower EDP, larger EF, and lower expression of BNP, compared with the EPO-H group. These anti-remodeling effects of EPO-L may result from the angiogenesis induced by EPO.

In the previous studies, several doses of EPO (1000 – 5000 U/kg) as a single administration significantly reduced myocardial infarction (13 – 17). Parsa et al. found that the infarct size in the rabbits treated with a single dose of 1000 U/kg was equally reduced and similar to that in those with 5000 U/kg (16). In the present study, we did not find any significant difference between the infarct size of EPO-L group and EPO-H group. In the present study, we also showed that a lower dose of EPO may be effective for treatment of MI.

In conclusion, we have demonstrated that EPO can reduce MI size and prevent cardiac remodeling and cardiac dysfunction after MI. Long-term treatment with low doses of EPO after MI increases capillary number to a greater extent than does short-term treatment. The expression of cardiac remodeling-related genes is likely to be lower after MI with long-term EPO treatment. Thus, long-term treatment for MI with low doses of EPO may be an effective therapeutic strategy for angiogenesis and prevention of cardiac remodeling.

Acknowledgments

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Coronary Flow Velocity Reserve Measurement in Three Major Coronary Arteries Using Transthoracic Doppler Echocardiography

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Background: Measurement of the coronary flow velocity reserve (CFVR) by transthoracic Doppler echocardiography (TTDE) has been reported to be useful for the noninvasive assessment of significant coronary artery stenosis or myocardial ischemia. The purpose of this study was to evaluate the value of this method in three major coronary arteries for detecting myocardial ischemia in the clinical setting. Methods: We studied 89 consecutive patients who were referred to our outpatient clinic because of chest pain. We measured CFVR using TTDE in three major coronary arteries. We defined CFVR < 2.0 in at least one vessel as being positive for myocardial ischemia. The accuracy of CFVR measurements for detecting myocardial ischemia was determined in comparison with exercise thallium-201 (Tl-201) single photon emission computed tomography (SPECT) as a reference standard. Results: CFVR in at least one vessel was successfully measured in 87 of 89 patients (98%). The sensitivity and specificity of CFVR < 2.0 in at least one coronary vessel, in any of the coronary territories, was 86% and 89%, respectively. In terms of assessing myocardial ischemia in each coronary artery territory, the agreement between CFVR < 2.0 and Tl-201 SPECT for the left anterior descending coronary artery, the posterior descending coronary artery, and the left circumflex coronary artery territories was 95%, 81%, and 73%, respectively. Conclusion: Noninvasive CFVR measurement by TTDE may be useful for detecting myocardial ischemia, as well as for identifying ischemic territories in the clinical setting. (ECHOCARDIOGRAPHY, Volume 23, April 2006)

coronary flow velocity reserve, myocardial ischemia, transthoracic Doppler echocardiography

Several noninvasive methods have been applied in the clinical setting for the detection of significant coronary stenosis or myocardial ischemia in outpatient clinics. Recently, transthoracic Doppler echocardiography (TTDE) has provided a noninvasive method for the assessment of coronary flow velocity reserve (CFVR) in three of the major coronary arteries. Measurement of CFVR in the left anterior descending coronary artery (LAD) by TTDE has been reported to be useful for the noninvasive assessment of significant LAD stenosis, when compared with quantitative coronary angiography.[1,2] Furthermore, it has also been used for the noninvasive detection of myocardial ischemia in the LAD territory and evaluated as an alternative to exercise thallium-201 (Tl-201) single photon emission computed tomography (SPECT).[3] Recent reports have shown that CFVR measurement in the posterior descending coronary artery (PDA) by TTDE is useful for the assessment of significant right coronary artery stenosis[4] and myocardial ischemia in the left ventricular (LV) inferior segments.[5] Furthermore, it has been reported that CFVR measurement in the left circumflex coronary artery (LCX) can detect significant stenosis and myocardial ischemia of the LCX.[6] If CFVR measurement by TTDE is applied to these three major coronary arteries in each patient, it may be possible to detect myocardial ischemia or significant coronary stenosis noninvasively in outpatients with chest pain. The purpose of this study was to evaluate the value

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of noninvasive CFVR measurement by TTDE in three major coronary arteries for detecting myocardial ischemia, as well as for identifying ischemic territories in outpatients with chest pain.

Methods

Study Population

We studied 89 consecutive patients (mean age 66 ± 9 years; 69 men and 20 women) who were scheduled for the Tl-201 SPECT because of chest pain suggesting angina pectoris by cardiologists. Exclusion criteria were LV wall-motion abnormality, previous myocardial infarction, LV hypertrophy, previous cardiac surgery, atrial fibrillation, significant valvular heart disease, and unstable angina. All patients continued administration of anti-ischemic medication (nitrates, beta blockers, calcium antagonists) and antiplatelet agents (aspirin, 81 mg) on the day of echocardiographic study. We obtained informed consent from all participants for following the study protocol, which was approved by the Committee for the Protection of Human Subjects in Research at Osaka City University Medical School.

Transthoracic Doppler Echocardiography

Transthoracic echocardiography was performed with a digital ultrasound system (ACUSON Sequoia 512, Siemens Medical Solutions USA, Inc. Ultrasound Division, Mountain View, CA), with a high frequency transducer (7V3c transducer, Doppler frequency 5–7 MHz) in the LAD, and a low frequency transducer (3V2c transducer, Doppler frequency 2–3 MHz) in the PDA and the LCX. For color Doppler flow mapping, the velocity range was set in the range of ±12 to ±24 cm/s. The color gain was adjusted to provide optimal images. In cases in which visualization of color signal on the coronary flow was insufficient or Doppler spectral tracing of the velocity was not clear, an echocardiographic contrast agent (Levovist, Schering, Berlin, Germany) was administered both at baseline and during hyperemic conditions as a Doppler enhancer. In accordance with the previous studies, we used a concentration of 300 mg/ml. The infusion rate was adjusted in the range of 2.0–0.5 ml/min according to the quality and entity of the Doppler signal enhancement achieved.[2,7,8] We tried to measure CFVR in each coronary artery within 15 minutes, in all studies within 45 minutes. All measurements were continuously recorded on half-inch S-VHS video tape, and the stopped frames of spectral Doppler signals were stored digitally on magneto-optical disks (540 MB) for subsequent offline analysis.

Measurements of the LAD Flow

Echocardiographic images were obtained from the acoustic window around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. After the lower portion of the interventricular sulcus had been located in the long-axis cross section, the ultrasound beam was rotated laterally, visualizing the distal portion of the LAD under color flow-mapping guidance. Color flow was visualized using a high frequency color Doppler technique. Blood flow velocity was measured by pulsed-wave Doppler echocardiography, using a sample volume (1.5–2.0 mm) placed on the color signal in the distal LAD. We tried to align the direction of the ultrasound beam to make it as parallel as possible with the distal LAD flow (Fig. 1A).

Measurements of the PDA Flow

For color Doppler identification and flow velocity measurement, we selected the PDA. After an optimal 2-dimensional image had been obtained in the apical four-chamber view, the transducer was rotated in a counterclockwise manner until the posterior interventricular sulcus was clearly visualized. Next, linear color signals, which persisted throughout diastole, were searched carefully in the posterior interventricular sulcus under the guidance of Doppler color flow mapping. A sample volume (1.5–2.0 mm) was positioned on the color signal in the PDA, and then blood flow velocity was recorded by pulsed-wave Doppler echocardiography (Fig. 1B).

Measurements of the LCX Flow

We searched Doppler flow signals of the LCX as linear color signals persisting during diastole on the base-to-mid portion of the LV lateral region in the apical four-chamber view as much as possible. It is likely that we detected the mid-to-distal LCX on the LV lateral region in the apical four-chamber view. Then, Doppler spectral tracings of LCX flow velocities were recorded by fast Fourier transformation analysis with a sample volume positioned on the most clearly visualized color signals (Fig. 1C).

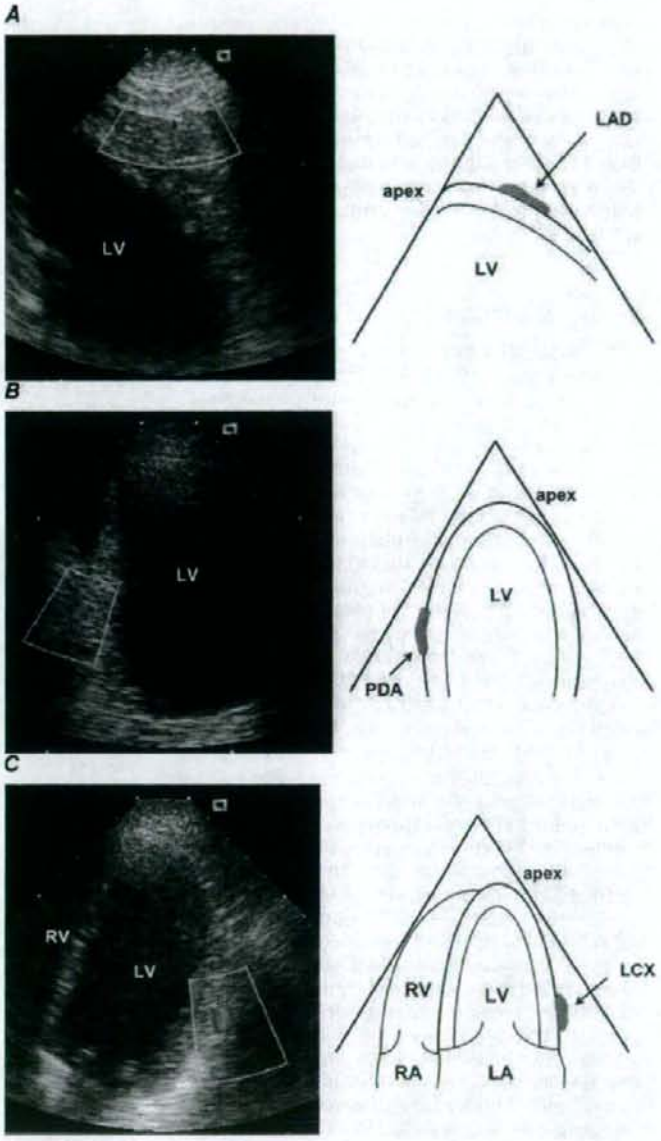

Figure 1. A. *Transthoracic color Doppler echocardiography demonstrating coronary blood flow (left) and schematic representation (right) in the distal LAD.* **B.** *Transthoracic color Doppler echocardiography demonstrating coronary blood flow (left) and schematic representation (right) in the PDA.* **C.** *Transthoracic color Doppler echocardiography demonstrating coronary blood flow (left) and schematic representation (right) in the LCX.*

CFVR Measurements by TTDE

Adenosine triphosphate (ATP) was administered by i.v. infusion (0.14 mg/kg per minute) for 2 minutes to record spectral Doppler signals during hyperemia. All patients had continuous monitoring of heart rate and blood pressure at baseline and during hyperemia. An experienced operator, blinded to the patient's data, measured coronary flow velocities. Both mean and peak diastolic flow velocities at baseline and at peak hyperemia were measured by tracing the

contour of the spectral Doppler signals manually using analysis software incorporated into the ultrasound system. An average of the measurements was obtained in three cardiac cycles. CFVR was calculated as the ratio of hyperemic to basal mean and peak diastolic flow velocities. Mean CFVR < 2.0 was defined as being positive for myocardial ischemia, on the basis of the results of previous studies that evaluated flow velocities.[9,10]

Exercise Tl-201 SPECT

Thallium-201 SPECT was performed within 1 week of the CFVR by TTDE studies. All patients performed symptom-limited exercise on a bicycle ergometer in the sitting position. Twelve-lead electrocardiograms and blood pressure measurements were obtained at baseline and every minute during exercise. The initial workload was 50 W, which was increased by 25 W every 2 minutes until an endpoint was reached. The endpoints included excessive fatigue, dyspnea, dizziness, angina, hypotension, diagnostic ST segment depression (>1.5 mm horizontal or downsloping or >2.0 mm upsloping), or significant arrhythmia. At peak exercise, a dose of 111 MBq of Tl-201 was injected intravenously. Initial SPECT images were obtained immediately after the termination of exercise and delayed images were obtained 4 hours later. SPECT was performed using a single head gamma scintillation camera equipped with a low energy, all-purpose, parallel-hole collimator. Thirty-two equidistant projections were acquired over 180° from the right anterior oblique to the left posterior oblique view at 25 s/projection. On the SPECT images, anteroseptal and apical segments were considered to be in the LAD territories. In the same way, inferior segments were the PDA territories, lateral-including posterior segments were the LCX territories. Two experienced nuclear physicians, who had no knowledge of the angiographic or echocardiographic data, analyzed each SPECT image individually. Disagreements in interpretations were resolved by consensus between the two physicians. Patients were considered to have myocardial ischemia when Tl-201 SPECT revealed perfusion defects with redistribution on delayed imaging. Combination of reversible perfusion defect and worsening of LV regional wall motion by exercise was used for the detection of multivessel coronary artery disease.[11,12]

Statistical Analysis

The study patients were classified into two groups according to the results of Tl-201 SPECT: group A with abnormal perfusion in any of the coronary territories, and group B with normal perfusion. Parametric data were presented as the mean value ± SD. Categorical variables were compared using the Fisher exact test. Echocardiographic and hemodynamic variables during ATP infusion between groups A and B were evaluated by two-way repeated measures analysis of variance (ANOVA), testing for group effect, ATP effect, and interaction. The Fisher-protected least significant difference test was used for post hoc testing. Mean and peak CFVR values for groups A and B were compared by the unpaired *t*-test. For all analysis, $P < 0.05$ was considered significant. The sensitivity, specificity, positive predictive value, and negative predictive value of CFVR were calculated in the traditional manner, as a predictor of abnormal perfusion on the Tl-201 SPECT image. Interobserver and intraobserver variabilities were assessed for CFVR measurement in 8 randomly selected patients. Interobserver variability was calculated as the SD of the differences between the measurements of two independent observers blinded to other patient data and expressed as a percentage of the average value. Intraobserver variability was calculated as the SD of the differences between the first and second determination, 15 minutes apart, for a single observer and expressed as a percentage of the average value.

Results

Of the 89 study patients, it was possible to evaluate CFVR in 87 patients (98%) in at least one vessel's territory. In 55 of 89 patients it was possible to calculate the CFVR in all the three vessels, in 25 in two vessels (15 patients both in the LAD and the PDA, 10 both in the LAD and the LCX), in 7 only in the LAD and in 2 in no vessels. The final study analysis was performed on 87 patients in whom CFVR was evaluated in at least one vessel's territory. No significant difference in age or gender was found between groups A and B (Table I).

Thallium-201 SPECT

All patients in this study performed exercise tests until the endpoints were reached. Using Tl-201 SPECT, 42 of the 87 patients (48%) qualitatively exhibited an abnormal perfusion in any

TABLE I
Clinical Characteristics

	All Patients (n = 87)	Group A (n = 42)	Group B (n = 45)
Age (years)	66 ± 9	66 ± 9	67 ± 9
Male	67 (77%)	35 (83%)	32 (71%)
Coronary risk factors			
Hypertension	53 (61%)	23 (55%)	30 (67%)
Smoking	55 (63%)	28 (67%)	27 (60%)
Diabetes	28 (32%)	13 (31%)	15 (33%)
Hyperlipidemia	37 (43%)	17 (40%)	20 (44%)

Data are presented as the mean value ± SD or number of patients.
There are no significant differences between the two groups.

territories and were classified as group A. The remainder of the patients (n = 45) had normal perfusion in all territories and were classified as group B. The peak heart rate and rate-pressure product were similar in groups A and B for all exercise tests.

Hemodynamic Data

No patient developed serious adverse effects, such as angina, atrioventricular block, nausea, flushing, or palpitations during the administration of ATP. Two-way repeated measures ANOVA showed no significant differences or interactions in terms of heart rate, systolic blood pressure, and diastolic blood pressure between groups A and B during administration of ATP.

CFVR Estimated by TTDE Versus Tl-201 SPECT

Only 6 patients in group A had mean CFVR ≥ 2.0, whereas 5 patients from group B had mean CFVR < 2.0. Mean CFVR < 2.0 in at least one coronary vessel predicted a reversible perfusion defect in any of the coronary territories, with a sensitivity of 86% and a specificity of 89% (Fig. 2A).

CFVR in the LAD Measured by TTDE Versus Tl-201 SPECT

Adequate spectral Doppler recordings of the LAD were obtained in 87 patients (98%). Mean CFVR < 2.0 predicted a reversible perfusion defect in the LAD territories, with a sensitivity of 95% and a specificity of 92% (Fig. 2B).

CFVR in the PDA Measured by TTDE Versus Tl-201 SPECT

Adequate spectral Doppler recordings of the PDA were obtained in 70 patients (79%). Mean CFVR < 2.0 predicted a reversible perfusion defect in the PDA territories, with a sensitivity of 81% and a specificity of 83% (Fig. 2C).

CFVR in the LCX Measured by TTDE Versus Tl-201 SPECT

Adequate spectral Doppler recordings of the LCX were obtained in 65 patients (73%). Mean CFVR < 2.0 predicted a reversible perfusion defect in the LCX territories, with a sensitivity of 73% and a specificity of 94% (Fig. 2D).

Observer Variability

Interobserver and intraobserver variabilities for CFVR measurements were 5.1% and 4.2%, respectively.

Discussion

In the present study, we evaluated the value of the CFVR using TTDE in three major coronary arteries for the detection of myocardial ischemia in outpatients with chest pain. TTDE was shown to be a feasible method for the noninvasive measurement of the CFVR in at least two vessel's territories and to be useful for the detection of myocardial ischemia in outpatients with chest pain.

Detection of Myocardial Ischemia in Outpatients with Chest Pain

Myocardial scintigraphy has been used as a screening tool for detecting coronary artery disease, particularly myocardial ischemia, because it is accurate and noninvasive method.[13–16] In scintigraphy, however, there are disadvantages, such as exposure to radioisotopes, high expensive of the procedure, and long recording times. TTDE overcomes these disadvantages.

Detection of Myocardial Ischemia by Echocardiography

Recently, technological improvements in TTDE have permitted noninvasive CFVR measurement in the distal LAD.[1–3,7] CFVR measurement by TTDE with a low frequency transducer provides data equivalent to that obtained using Tl-201 SPECT for myocardial ischemia

A

	CFR < 2.0	CFR ≧ 2.0	
Group A	36	6	42
Group B	5	40	45
	41	46	87

B

	LAD CFR < 2.0	LAD CFR ≧ 2.0	
SPECT positive	20	1	21
SPECT negative	5	61	66
	25	62	87

C

	PDA CFR < 2.0	PDA CFR ≧ 2.0	
SPECT positive	13	3	16
SPECT negative	9	45	54
	22	48	70

D

	LCX CFR < 2.0	LCX CFR ≧ 2.0	
SPECT positive	11	4	15
SPECT negative	3	47	50
	14	51	65

Figure 2. A. *The correlation between CFVR and the results of Tl-201 SPECT. The sensitivity and specificity of CFVR < 2.0 in at least one coronary vessel for the detection of myocardial ischemia in any coronary territories were 86% and 89%, respectively.* **B.** *The correlation between CFVR and the results of Tl-201 SPECT for the LAD territories. The sensitivity and specificity of CFVR < 2.0 in the distal LAD for the detection of myocardial ischemia in the LAD territories were 95% and 92%, respectively.* **C.** *The correlation between CFVR and the results of Tl-201 SPECT for the PDA territories. The sensitivity and specificity of CFVR < 2.0 in the PDA for the detection of myocardial ischemia in the PDA territories were 81% and 83%, respectively.* **D.** *The correlation between CFVR and the results of Tl-201 SPECT for the LCX territories. The sensitivity and specificity of CFVR < 2.0 in the LCX for the detection of myocardial ischemia in the LCX territories were 73% and 94%, respectively.*

in the LV inferior region.[5] Furthermore, CFVR measurement in the LCX using TTDE with an i.v. contrast agent can estimate myocardial ischemia in the LV lateral regions.[6] However, there have been no reports evaluating the value of CFVR measurement by TTDE in three major coronary arteries for the detection of myocardial ischemia. Thus, we designed the present study to evaluate the value of CFVR measured by TTDE for the detection of myocardial ischemia in outpatients with chest pain.

Of the 89 study patients, it was possible to evaluate CFVR in 87 patients (98%) in at least one vessel's territory. It was possible to evaluate CFVR in 80 patients (90%) in at least two vessel's territories. Thus, CFVR measurements by TTDE were feasible in the present study population who visited the outpatient clinic because of chest pain. In all of the study patients, CFVR measured by TTDE enabled accurate physiologic assessment of coronary artery stenosis and predicted the results of Tl-201 SPECT (86% sensitivity and 89% specificity). These results suggest that the present method may be useful for the clinical evaluation of myocardial ischemia and in outpatients with chest pain.

Advantages of Transthoracic Doppler Assessment

The present noninvasive method may have several advantages. First, CFVR measured by TTDE enables accurate physiologic assessment of coronary artery stenosis in patients with chest pain, and predicts the results of Tl-201 SPECT with high sensitivity and specificity.

Second, a potential limitation of Tl-201 SPECT is that a measurement of relative, rather than absolute, myocardial blood flow is

obtained. On the other hand, CFVR measurement by TTDE can be applied to these three major coronary arteries in each of the vessel territories. Thus, it may be more suitable for detecting myocardial ischemia in individual territories.

Finally, CFVR measurement by TTDE is noninvasive and inexpensive compared to measurements obtained using Tl-201 SPECT for myocardial ischemia in any of the vessel territories. This result expands the usefulness of this method in the assessment of angina pectoris.

Study Limitations

First, there were some technical limitations of noninvasive CFVR measurement by TTDE. Regarding CFVR measurement in the LAD, flow in the LAD branches could be erroneously interpreted as the flow in the main trunk.[8] In addition, it was more difficult to measure CFVR in the PDA or the LCX than in the LAD. But it has been reported that i.v. contrast agents helped to detect the PDA or the LCX flow.[5,6] Actually, in 30 patients (34%) in which visualization of color signal or Doppler spectral tracing of velocity was unsuccessful, an echocardiographic contrast agent was used to improve the success rate in the present study. Furthermore, addition with the distance between signals and echo probe, artifacts from the lung could affect coronary flow recordings on the LCX.[6] Finally, if the sample volume of the Doppler is placed proximal to a distal stenosis, this would result in false negative in CFVR measurements.

Second, it is difficult to detect multivessel coronary artery disease even with the "gold standard" Tl-201 SPECT. However, in this study, we used the combined assessment of worsening of LV regional wall motion by exercise and perfusion data in Tl-201 SPECT for the detection of multivessel coronary artery disease, which is more accurate than the conventional methods.[11]

Third, there were several exclusion criteria in CFVR measurements, not normally excluded from Tl-201 SPECT. This is an important limitation in this method for the diagnosis of myocardial ischemia. However, CFVR measurements also have advantages, such as no exposure to radioisotopes, shorter recording time than Tl-201 SPECT.

Fourth, microvascular dysfunction due to diabetes mellitus, hypertension, hyperlipidemia, and smoking can affect CFVR values.[17–20] However, a recent paper has shown that a cutoff value of < 2.0 for the CFVR as measured by TTDE was adequate for the diagnosis of significant coronary stenosis in a population including patients with coronary risk factors.[21] This report confirmed that a CFVR of < 2.0 is a useful cutoff value for noninvasive assessment of significant coronary stenosis in routine clinical examinations.

Finally, in this study, prognostic data were not included regarding CFVR measurement. Whether this method will lead to therapeutic alterations or will predict patient outcomes requires additional investigations.

Conclusions

There is a high correlation for detecting myocardial ischemia between noninvasive CFVR measurement in three major coronary arteries using TTDE and Tl-201 SPECT in patients with chest pain. Thus noninvasive CFVR measurement by TTDE may be useful for detecting myocardial ischemia, as well as for identifying ischemic territories in the clinical setting.

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Beta-Blocker Therapy Induces Ventricular Resynchronization in Dilated Cardiomyopathy With Narrow QRS Complex

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Objectives We sought to evaluate the effects of beta-blocker therapy on regional and global myocardial mechanics in addition to ventricular synchrony in patients with heart failure and normal QRS by using tissue Doppler and strain echocardiography.

Background It is unknown whether beta-blocker therapy can influence mechanical synchrony.

Methods Conventional and strain echocardiography were performed in 15 healthy age-matched volunteers and in 25 patients with idiopathic dilated cardiomyopathy (IDC). Of these, 15 IDC patients on standard heart failure therapy were studied prior to and at 1 and 6 months after initiation of carvedilol therapy and compared to the controls.

Results There was significant mechanical dyssynchrony in IDC compared with control patients. Patients placed on carvedilol demonstrated a significant decrease in the inferoseptal to lateral wall delay in peak strain (normalized to the R-R interval) between baseline and 1 month and between baseline and 6 months. Similarly, global time to peak segmental strain (455 ± 51 ms vs. 423 ± 59 ms, respectively, $p = 0.02$, and 455 ± 51 ms vs. 415 ± 50 ms, respectively, $p = 0.01$) and the coefficient of variation of the time to peak segmental strain decreased (17 ± 4% vs. 15 ± 5%, respectively, $p = 0.02$, and 17 ± 4% vs. 14 ± 5%, respectively, $p = 0.03$), from baseline to 1 month and between baseline and 6 months, respectively. Global strain significantly increased from baseline to 1 month (−8.2 ± 1.8 to −10.4 ± 3.9, respectively, $p = 0.01$) and between baseline and 6 months (−8.2 ± 1.8% to −12.0 ± 3.2%, respectively, $p = 0.008$). Improvements in left ventricular ejection fraction and reverse remodeling were coincident with reductions in mechanical dyssynchrony.

Conclusions The use of carvedilol improves contractile function and dyssynchrony in heart failure patients with normal QRS.
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A significant proportion of patients with heart failure (HF) develop conduction abnormalities (1). Intraventricular dyssynchrony appears to play a major pathophysiologic role in HF, as suggested by the substantial clinical improvements observed after cardiac resynchronization therapy (CRT) through biventricular pacing (2,3). As a result, CRT has emerged as a promising treatment for medically refractory heart failure. Published data suggest that CRT improves patient symptom and quality of life, induces reverse remodeling, positively impacts neurohumoral pathways, and may improve outcomes and survival (4,5). The presence of significant intraventricular synchrony appears to predict a patient's response to CRT (5,6).

All large CRT clinical trials primarily enrolled patients with significant prolongation of the QRS complex (>120 ms) (7,8). However, more recent data demonstrate that a proportion of HF patients with narrow QRS complexes also demonstrate significant intraventricular dyssynchrony as detected by tissue Doppler echocardiography (TDE) (9) There is a growing clinical conundrum as to whether patients with HF and narrow QRS complexes but significant ventricular dyssynchrony on TDE (heart failure + narrow QRS [HF-N]) would benefit from CRT. Decisions to treat HF-N patients with CRT devices have obvious clinical and economic implications.

Clinical trials have shown that medical therapy (e.g., beta-blockers) can induce morphologic reverse remodeling in patients with HF. However, it is unknown whether

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medical therapy can influence mechanical synchrony. Intuitively, beta-blocker therapy may worsen conduction abnormalities in patients and, therefore, dyssynchrony. Intraventricular synchrony is most commonly assessed using TDE, which is used to measure local tissue velocities and can accurately depict regional myocardial mechanical activity. Tissue Doppler-derived strain echocardiography (SE) depicts regional deformation and may be superior to TDE because it is less susceptible to translational and tethering artifacts (10). Accordingly, the present study sought to examine changes in ventricular function and mechanical synchrony using SE in HF-N patients receiving carvedilol therapy.

Methods

Study group. All patients and healthy volunteers provided informed consent, and the protocol was approved by the committee on clinical investigation of Osaka City University Institutional Review Board. We prospectively and consecutively enrolled patients with idiopathic dilated cardiomyopathy (IDC). Inclusion criteria were ejection fraction (EF) <40%, narrow QRS <120 ms, normal sinus rhythm, no significant coronary artery stenosis confirmed by coronary angiography, and no prior administration of beta-blocker therapy. We excluded patients with significant valvular heart disease, a history of cardiac surgery, pacemaker implantation, congenital heart disease, secondary cardiomyopathy, atrial fibrillation, and QRS width exceeding 120 ms. All patients were clinically stable and on stable medical therapy, including angiotensin-converting enzyme inhibitor or angiotensin II receptor blockades and diuretics. All medication doses were optimized before enrollment and remained unchanged during the study. Healthy volunteers were solicited via campus advertisements and were individuals with no cardiac history, who were not on any cardioactive medications (including carvedilol), and who had a normal screening echo-Doppler examination. Controls were age-matched such that there was one control for every patient.

Beta-blocker therapy. Carvedilol was initiated after initial echocardiographic examination in 15 patients with IDC. The starting dose was 2.5 or 5 mg/day, which was titrated upwards to a target dose of 20 mg/day or maximum tolerated dose. The control group subjects did not receive any medications.

Echocardiography. All patients and controls underwent standard, comprehensive 2-dimensional (2D) and Doppler echocardiography at enrollment. Additionally, 15 patients with IDC were studied at 1 and 6 months after the initiation of carvedilol therapy. Left ventricular (LV) end-diastolic volume, end-systolic volume, and EF (biplane Simpson's formula) were determined. All patients underwent TDE and SE at the same time points as conventional echocardiography. All age-matched healthy volunteers underwent standard, comprehensive 2D and Doppler echocardiography, TDE, and SE at a single time point. All imaging was performed using a Vivid 7 ultrasound system (GE Ultrasound, Horten, Norway). Standard views were used for conventional echocardiography. For TDE and SE, single walls were imaged in 3 apical views, at high frame rates (170 to 200 frames/s) using a narrow sector angle with the wall parallel to the ultrasound beam (10). At least 3 consecutive beats were obtained, and the images were stored digitally for offline analysis. All TDE and SE parameters were analyzed per segment using a standard 12-segment (American Society of Echocardiography) model. A strain offset length of 8 mm was used for all measurements. Systolic strain tracings from 3 cardiac cycles were obtained of each segment and averaged to yield a final strain curve. Peak systolic strain (segmental ϵ) and time from the R-wave of the ECG trace to peak systolic strain (segmental Tϵ) were measured on the averaged strain curve of each segment. All segmental Tϵ values were corrected for the heart rate using Bazett's formula to avoid the confounding influence of changes in heart rate during carvedilol therapy. Segmental ϵ values were averaged over the course of 12 segments to yield a global ϵ value (global ϵ). The coefficient of variation of segmental ϵ values (CVϵ) was used as an index of heterogeneity of segmental mechanical contraction. The CVϵ was obtained by dividing the standard deviation by the mean of segmental ϵ values. Segmental Tϵ values were averaged over the course of 12 segments to yield a global Tϵ value (global Tϵ). The coefficient of variation of segmental Tϵ (CVTϵ) was used as a measure of intraventricular dyssynchrony. The CVTϵ was calculated by dividing the standard deviation by the mean of segmental Tϵ values.

Statistics. All values were expressed as mean ± SD. The Friedman test was used to compare the 3 time points, followed by the Wilcoxon signed-rank test in case of significance. A value of $p < 0.05$ was considered to indicate statistical significance. Simple comparison-wise p values derived from the Wilcoxon signed-rank test are reported in the tables and figures. Interobserver and intraobserver variability for both segmental Tϵ and segmental ϵ were measured by analysis of 4 randomly selected patients (144 segments) and 4 randomly selected healthy volunteers (48

Abbreviations and Acronyms

CV = coefficient of variation

CVϵ = coefficient of variation of segmental ϵ values

CVTϵ = coefficient of variation of segmental Tϵ

global ϵ = averaged segmental strain values over 12 segments

global Tϵ = averaged segmental Tϵ values over 12 segments

HF = heart failure

HF-N = heart failure with narrow QRS complex (<120 ms)

IDC = idiopathic dilated cardiomyopathy

SE = tissue Doppler derived strain echocardiography

segmental ϵ = peak systolic strain in a segment

segmental Tϵ = time from the R-wave of the electrocardiogram trace to peak systolic strain in a particular segment

TDE = tissue Doppler echocardiography

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segments) by 2 independent blinded observers. All results were compared by linear least-squares regression analysis. Limits-of-agreement analysis by the methods of Bland and Altman also was performed.

Results

We enrolled 25 patients with IDC and 15 healthy controls. Of these, 19 patients were enrolled consecutively, whereas 10 additional patients were enrolled later. Four patients did not complete the study protocol (1 died during the follow-up, 1 developed left bundle branch block during the follow-up, and 2 were lost to follow-up). Therefore, cross-sectional data were available in 25 patients with IDC and 15 control patients. Longitudinal data were available from 15 patients with IDC. Baseline characteristics of the patients with IDC who were followed longitudinally are given in Table 1. The mean maintenance dose of carvedilol was 11 ± 6 mg/day.

Hemodynamic and echocardiographic parameters. Hemodynamic and echocardiographic data are summarized in Table 2. There was no significant change in systolic and diastolic blood pressures during the study. There was significant decrease in heart rates from baseline to 1 month (84 ± 12 beats/min vs. 72 ± 9 beats/min, respectively, $p = 0.001$) with no further significant change at 6 months.

There were no significant reductions in LV end-diastolic and end-systolic volumes at 1 month. However, there were significant reductions in end-diastolic (193 ± 70 ml vs. 156 ± 68 ml, respectively, $p = 0.008$) and end-systolic volumes (140 ± 58 ml vs. 105 ± 65 ml, respectively, $p = 0.006$) between baseline and 6 months.

Although there was a nonsignificant trend toward an increase in left ventricular ejection fraction between baseline and 1 month (28 ± 6% vs. 31 ± 7%, $p = 0.06$), there was a significant increase in left ventricular ejection fraction between baseline and 6 months (28 ± 6% vs. 37 ± 10%, respectively, $p = 0.004$).

Table 2 Hemodynamic and Echocardiographic Parameters

	Baseline	1 Month	6 Months
Hemodynamic parameters			
SBP (mm Hg)	105 ± 13	103 ± 11	109 ± 17
DBP (mm Hg)	68 ± 9	64 ± 7	66 ± 11
HR (beats/min)	84 ± 12	72 ± 9*	70 ± 8*
Echocardiographic parameters			
EDV (ml)	193 ± 70	186 ± 76	156 ± 68*
ESV (ml)	140 ± 59	135 ± 67	104 ± 65*
EF (%)	28 ± 6	31 ± 7	37 ± 10*

Values are mean ± SD. *$p < 0.05$ versus baseline.
DBP = diastolic blood pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HR = heart rate; SBP = systolic blood pressure.

Strain echocardiography. There was significant dyssynchrony in the IDC patients with narrow QRS complexes ($n = 25$) compared with the normal controls ($n = 15$). Global $T\epsilon$ was 457 ± 56 ms versus 348 ± 24 ms ($p < 0.0001$), CV segmental $T\epsilon$ was 18 ± 4% versus 7 ± 3% ($p < 0.0001$), global ϵ was −8.1 ± 1.8% versus −18.5 ± 1.3% ($p < 0.0001$), and CV segmental ϵ was 43 ± 10% versus 14 ± 3% ($p < 0.0001$), respectively (IDC vs. controls). These data confirm the presence of dyssynchrony in IDC patients with narrow QRS complex compared with normal healthy volunteers.

Figure 1 displays representative myocardial strains at the LV midinferoseptal and midlateral segments at baseline, 1 month, and 6 months. There was a significant decrease in the inferoseptal to lateral wall delay in segmental $T\epsilon$ between baseline and 1 month (103 ± 51 ms vs. 70 ± 45 ms, respectively, $p = 0.02$) and baseline and 6 months (103 ± 51 ms vs. 51 ± 46 ms, respectively, $p = 0.002$).

Table 3 demonstrates EF and SE parameters in healthy volunteers and the temporal changes in patients with IDC. The EF and all SE parameters in healthy volunteers were significantly different from those in patients with IDC at baseline, 1 month, and 6 months. In patients with IDC, there

Table 1 Baseline Characteristics

Patient #	Age, yrs	Gender	SBP	DBP	HR	BSA	CAD on CAG	ACEI or ARB	Digoxin	Diuretics
1	49	M	92	64	84	1.90	No	Yes	No	Yes
2	75	F	86	56	80	1.25	No	Yes	No	Yes
3	29	M	102	68	96	2.18	No	Yes	No	Yes
4	65	M	120	86	80	1.63	No	Yes	No	Yes
5	31	M	110	80	88	1.84	No	Yes	No	Yes
6	66	M	122	76	64	1.61	No	Yes	No	Yes
7	53	M	110	76	88	1.80	No	Yes	No	Yes
8	72	M	110	60	80	1.56	No	Yes	No	Yes
9	46	M	114	76	92	1.95	No	Yes	No	Yes
10	65	F	102	64	72	1.34	No	Yes	No	Yes
11	75	F	118	66	86	1.45	No	Yes	No	Yes
12	69	M	94	60	88	1.49	No	Yes	No	Yes
13	58	F	84	54	60	1.36	No	Yes	No	Yes
14	55	F	120	72	96	1.59	No	Yes	No	Yes
15	70	F	94	60	69	1.54	No	Yes	No	Yes

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BSA = body surface area; CAD = coronary artery disease; CAG = coronary angiography; DBP = diastolic blood pressure; F = female; HR = heart rate; M = male; SBP = systolic blood pressure.

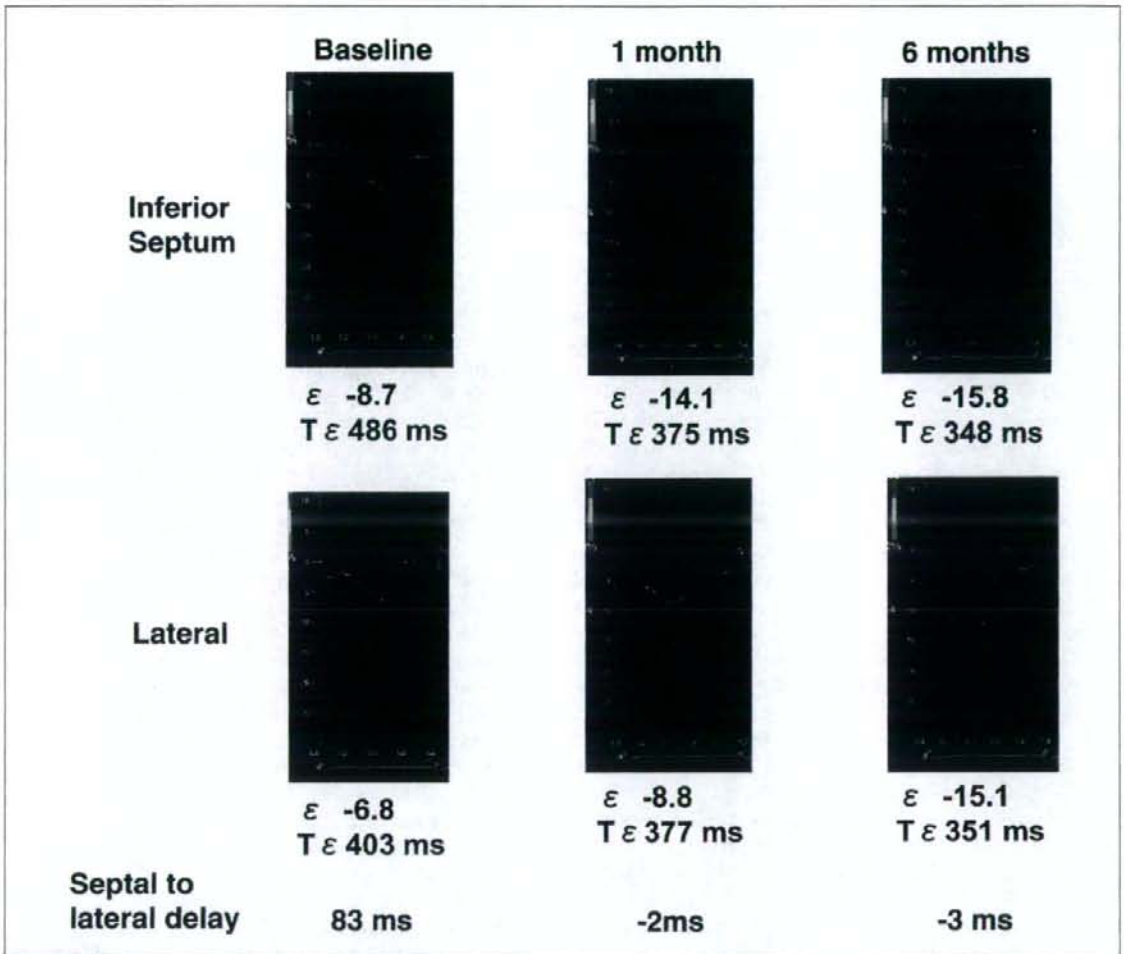

Figure 1 Representative Traces of Myocardial Strains

(Top) Myocardial strains of the left ventricular midinferoseptal segment: **left panels** = baseline; **middle panels** = 1 month; **right panels** = 6 months. **(Bottom)** Myocardial strains of the left ventricular midlateral segment. Inferoseptal to lateral wall delay in time from electrocardiographic peak R wave to peak systolic strain was 83 ms at baseline, −2 ms at 1 month, and −3 ms at 6 months.

was a significant decrease in global Tϵ from baseline to 1 month (455 ± 51 ms vs. 423 ± 59 ms, respectively, p = 0.02), and between baseline and 6 months (455 ± 51 ms vs. 415 ± 50 ms, respectively, p = 0.01). There were similar decreases in CV segmental Tϵ between baseline and 1 month (17 ± 4% vs. 15 ± 5%, respectively, p = 0.02) and between baseline and 6 months (17 ± 4% vs. 14 ± 5%, respectively, p = 0.03).

Global ϵ was significantly reduced in all subjects at baseline (mean global ϵ = −8.2 ± 1.8%). There was a significant increase in global ϵ from baseline to 1 month (−8.2 ± 1.8% to 10.4 ± 3.9%, respectively, p = 0.01) and between baseline and 6 months (−8.2 ± 1.8% to 12.0 ± 3.2%, respectively, p = 0.008). In contrast, there was no significant change in CV segmental ϵ between baseline and 1 month (44 ± 12% vs. 47 ± 22%, respectively, p = 0.38). However, CV segmental ϵ decreased significantly from baseline/1 month to 6 months (44 ± 12%/47± 22% vs. 33 ± 15%, respectively, p = 0.03). Table 3 demonstrates temporal changes of EF, global Tϵ, CV segmental Tϵ, global ϵ, and CV segmental ϵ. Parallel significant temporal changes can be seen only between EF and CV segmental ϵ, not between EF and CV segmental Tϵ or global ϵ. The normalization for heart rate was performed using Bazett's formula. In the absence of normalization, global Tϵ were as follows: volunteers at enrollment, 339 ± 24 ms; IDC patients at baseline, 386 ± 38 ms; IDC patients at 1 month, 388 ± 43

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Table 3 Ejection Fraction and Strain Echocardiographic Data

		IDC patients (n = 15)		
	Volunteers (n = 15)	Baseline	1 Month	6 Months
LVEF (%)	63 ± 5	28 ± 6	31 ± 7	37 ± 10*
Global $T\varepsilon$ (ms)	348 ± 24	455 ± 51	423 ± 59*	415 ± 50*
CV segmental $T\varepsilon$ (%)	7 ± 3	17 ± 4	15 ± 5*	14 ± 5*
Global ε (%)	−18.5 ± 1.3	−8.2 ± 1.8	−10.4 ± 3.9*	−12.0 ± 3.2*
CV segmental ε (%)	14 ± 3	44 ± 12	47 ± 22	33 ± 15*

*$p < 0.05$ when compared with baseline value.

CV segmental $T\varepsilon$ = coefficient of variation of segmental $T\varepsilon$ of 12 segments; CV segmental ε = coefficient of variation of segmental ε of 12 segments; LVEF = left ventricular ejection fraction; global $T\varepsilon$ = averaged segmental $T\varepsilon$ values over 12 segments; global ε = averaged segmental ε values over 12 segments; IDC = idiopathic dilated cardiomyopathy; segmental $T\varepsilon$ values = time to peak systolic strain corrected for heart rate; Volunteers = healthy volunteers matched for age.

ms; and IDC patients at 6 months, 386 ± 45 ms. Global $T\epsilon$ was significantly lower in volunteers at enrollment compared with IDC patients at baseline ($p = 0.0005$), at 1 month ($p = 0.0015$), and at 6 months ($p = 0.0024$), respectively. Global $T\epsilon$ was similar between IDC patients at all 3 time points. Coefficient of variation segmental $T\epsilon$ was as follows: volunteers at enrollment, 7 ± 3%; IDC patients at baseline, 17 ± 4%; IDC patients at 1 month, 15 ± 5%; and IDC patients at 6 months, 14 ± 5%. Coefficient of variation segmental $T\epsilon$ was significantly lower in volunteers at enrollment compared with IDC patients at baseline ($p < 0.0001$), at 1 month ($p = 0.0001$), and at 6 months ($p = 0.0010$), respectively. In patients with IDC, there was a significant decrease in CV segmental $T\epsilon$ from baseline to 1 month (17 ± 4% vs. 15 ± 5%, respectively, $p = 0.02$), and from baseline to 6 months (17 ± 4% vs. 14 ± 5%, respectively, $p = 0.03$).

Intraobserver and interobserver variability for segmental $T\epsilon$ measurement was 2.9% and 6.9%, respectively. Intraobserver and interobserver variability for segmental ϵ was 8.8% and 12.3%, respectively.

Discussion

Our data demonstrate that beta-blocker therapy induces significant reductions in intraventricular dyssynchrony in dilated cardiomyopathy patients with heart failure and normal QRS. Beta-blocker therapy is associated with an early (1 month) increase in regional systolic function (increased global ϵ) and a delayed decrease in mechanical dyssynchrony (decreased CVϵ). Improvements in LVEF and reverse remodeling are coincident with reductions in mechanical dyssynchrony. Reduction in ventricular dyssynchrony may be one of the mechanisms underlying the beneficial effects of beta-blockers in HF.

Intraventricular and interventricular dyssynchrony have emerged as important mechanisms contributing to the progression of heart failure and ventricular remodeling (2,3). Their emergence has resulted in CRT becoming a significant alternative in HF refractory to medical therapy in patients with evidence of abnormal conduction. Beta-blockers such as carvedilol are a critical component of HF therapy. However, the interaction between beta-blockers and dyssynchrony is uncertain. Furthermore, the effects of beta-blocker therapy on regional and global cardiac mechanics have not been previously examined. Carvedilol therapy has favorable effects on ventricular function, ventricular remodeling, heart failure symptoms, morbidity, and mortality (11–15). Although the precise mechanisms underlying these favorable effects have not been fully clarified at the whole heart level, several possible mechanisms include reduction of heart rate and/or afterload (16), alleviation of adverse neurohormonal effects (17), and antiapoptotic effects (18). To define the effects of carvedilol therapy on cardiac mechanics and dyssynchrony, we used tissue Doppler-derived strain echocardiography to interrogate regional and global myocardial function.

Tissue Doppler echocardiography and TDE-derived SE depict regional displacement and deformation (19,20). Both techniques have been extensively validated in the experimental and clinical setting (21–23). Because mechanical synchrony cannot be assessed adequately via conventional echocardiography, TDE and SE have become the mainstays of dyssynchrony interrogation. Detailed descriptions of SE have been previously published (20). Although most data regarding cardiac dyssynchrony have been generated using TDE, SE offers some advantages. Strain imaging is less susceptible to translational motion and tethering artifacts and may be useful in subjects with extensive wall motion abnormalities. Moreover, SE is superior to TDE in regional function analysis and was therefore more appropriate to accomplish our study objectives (10).

Our data demonstrate that carvedilol therapy significantly increases regional and global contractility as evidenced by an increase in ϵ and EF. Our data also clarify the changes in regional and global cardiac mechanics that potentially underlie the improvements in cardiac function seen from carvedilol therapy. Early after initiation of carvedilol therapy there appears to be an increase in regional contractility. These regional changes in systolic function may be explained by previously demonstrated restoration of the biological properties of the cardiac myocyte by carvedilol, including the reversal of high-energy phosphate production and normalization of calcium handling (24–27). Improvement of impaired coronary flow reserve by carvedilol may also contribute to the recovery of LV function (28).

However, it appears that the early increments in local contractility do not translate into an increment in global function, as seen by the absence of a significant change in EF. On the other hand, an improvement in intraventricular synchrony, that occurs several months later, is associated with an increase in EF. The increase in EF and reduction in dyssynchrony is coincident with echocardiographic evidence of reverse remodeling. The coordinated LV contraction resulting in improved chamber efficiency and reduced myocardial energy consumption observed in CRT also may underlie the global LV function improvements found with the use of carvedilol (29,30). Our data concerning resynchronization and reverse remodeling are concordant with those reported from CRT studies (4,5).

Study limitations. We excluded patients with ischemic cardiomyopathy. The effects of beta-blockers may be significantly different between patients with IDC and with ischemic cardiomyopathy. We only included IDC patients with QRS width <120 ms in this study. The effects of beta-blockers on dyssynchrony may be different in patients with more significant conduction disease (e.g., QRS >120 ms) and in patients with ischemia and/or significant myocardial scar.

Conclusions. Beta-blocker therapy stimulates increments in local contractility and reduction of intraventricular dyssynchrony. To our knowledge, this is the first report of cardiac resynchronization by medical therapy. Increased regional systolic function followed by cardiac resynchronization potentially underlies the beneficial effects of beta-blockers in heart failure.

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Relation of early improvement in coronary flow reserve to late recovery of left ventricular function after β-blocker therapy in patients with idiopathic dilated cardiomyopathy

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Background β-Blocker therapy reverses left ventricular (LV) remodeling in patients with idiopathic dilated cardiomyopathy (IDC). Improvement in coronary circulation by β-blocker could play a role in these circumstances. This study investigated the relationship between change in coronary flow reserve (CFR), as a marker of coronary circulation, and subsequent improvement in LV ejection fraction (LVEF) at follow-up during carvedilol therapy in patients with IDC.

Methods Eighteen patients with IDC underwent CFR measurements by transthoracic Doppler echocardiography at baseline and after 1 month of treatment with carvedilol. A follow-up echocardiographic assessment of LVEF was done at 12 ± 6 months of treatment. The patients were classified by the degree of improvement in LVEF in the follow-up study, as group A (LVEF change ≥10%) and group B (LVEF change <10%).

Results Although there was no significant difference in CFR between the 2 groups at baseline, CFR was significantly higher in group A than in group B at 1 month of therapy (3.7 ± 0.5 vs 2.5 ± 0.9; $P < .01$). Coronary flow reserve change after 1 month was significantly greater in group A than in group B (1.3 ± 0.6 vs 0.4 ± 0.5; $P < .01$). Logistic regression analysis revealed that CFR change predicted a significant improvement in LVEF at follow-up ($P < .05$). Furthermore, a significant correlation was found between the change in CFR after 1 month and that in LVEF on follow-up ($r = .65$, $P < .01$).

Conclusions This study demonstrated that early change in CFR is associated with subsequent improvement in LVEF, suggesting the potential predictive value of coronary circulation for subsequent LV reverse remodeling after β-blocker therapy in patients with IDC. (Am Heart J 2007;153:1080.e1-1080.e6.)

Administration of carvedilol, a third-generation β-adrenergic blocking agent, reduces morbidity and mortality in patients with left ventricular (LV) systolic dysfunction including that caused by idiopathic dilated cardiomyopathy (IDC).[1-7] β-Blocker is the only drug for heart failure to reverse LV remodeling.[7] Previous trials with carvedilol indicated that reversed LV remodeling correlates with improved survival.[1,6,7] However, not all patients have improved LV systolic function with β-blocker therapy and the mechanism of reversed LV remodeling by β-blocker remains unclear.

In patients with IDC, coronary flow reserve (CFR) as a marker of coronary circulation is impaired despite angiographically normal coronary arteries, which is attributable to coronary microvascular dysfunction.[8-14] According to the microvascular ischemic hypothesis in IDC, this impairment of CFR may induce intermittent periods of myocardial ischemia or repetitive stunning, subsequently affecting myocardial function and leading to chronic reversible LV dysfunction.[13-15] Recently, a preliminary study[16] demonstrated that carvedilol therapy improves impaired CFR earlier than it does LV systolic dysfunction in patients with IDC. Despite the absence of a significant change in LV ejection fraction (LVEF) after a short-term (<3 months) β-blocker therapy,[7,17] there is a rapid increase in CFR at that time.[16] However, although CFR improvement was observed after carvedilol therapy in the overall population in this preliminary study, there were some differences in the

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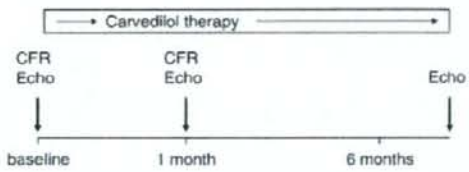
Figure 1



Study protocol.

degree of CFR improvement in each patient. We hypothesized that an absence of LV reverse remodeling during β-blocker therapy may be associated with that of early improvement in coronary circulation. Thus, the purpose of this study was to evaluate the relationship between early improvement in CFR and subsequent recovery of LV systolic function at follow-up in patients with IDC, as assessed by transthoracic Doppler echocardiography (TTDE).

Methods

Study patients

We studied 20 patients with IDC (14 men, 6 women; mean age 56 ± 15 years) who had not taken β-adrenergic blocking agents. All patients had clinically stable New York Heart Association class I to II symptoms. Each patient enrolled in the study met the following criteria: (1) normal sinus rhythm, (2) normal coronary arteries confirmed by coronary angiography or Tl-SPECT and (3) LVEF <40%, (4) LV end-diastolic diameter >55 mm. Patients were excluded from the study if they had a history of heavy alcohol abuse, severe hypertension, primary valvular heart disease, or any other known cause of dilated cardiomyopathy. All patients were stabilized by using an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and diuretic treatment for at least 1 month.

Study protocol

Patients received carvedilol in addition to their usual medications for heart failure. The starting dose of carvedilol was 2.5 or 5.0 mg/d, which was then gradually increased to a target dose of 20 mg/d or to a tolerated dose (12 ± 6 mg/d). A dose of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker was not changed in the follow-up period. Echocardiographic measurements including CFR measurement by TTDE were performed at baseline and at 1 month after administration of carvedilol. A follow-up echocardiographic assessment of LV function was performed at least after 6 months (12 ± 6 month) during treatment with carvedilol (Figure 1). Of the 20 patients enrolled in this study, we excluded 2 patients. One patient discontinued use of carvedilol and 1 died during follow-up. The patients reported in our previous study[16] were included in the present study. A retrospective analysis was performed based on change in LVEF from baseline on follow-up echocardiography. The cutoff value of LVEF change ≥10% was chosen according to the previous reports showing that improvement in LVEF ≥10% was used as a responder to β-blocker.[18,19] We divided the findings into 2 groups: group A, a significant improvement in LVEF (LVEF change ≥10%, n = 10), and group B, no significant improvement in LVEF (LVEF change <10%, n = 8). The study protocol was approved by the ethics committee of Osaka City University Medical School, and written informed consent was obtained from each patient.

Echocardiographic measurements

We used the Sequoia digital ultrasonography system (Siemens, Mountain View, CA) or the Vivid 7 digital ultrasonography system (GE Vingmed Ultrasound, Horten, Norway) for echocardiographic measurements. Left ventricular end-diastolic volume, end-systolic volume, and EF were calculated with the biplane Simpson formula.[20] Mitral inflow velocity wave was recorded by pulsed Doppler echocardiography, and E wave velocity, A wave velocity, E/A, and E wave deceleration time were measured.

Measurement of coronary flow velocity and coronary flow reserve

The measurements of CFR in the left anterior descending coronary artery (LAD) by TTDE were performed as previously described,[21,22] using high-frequency transducers (5.0-7.5 MHz on the Sequoia digital ultrasonography system, or 4.4-11.4 MHz on the Vivid 7 digital ultrasonography system). We first recorded a baseline spectral Doppler signal in the LAD. Adenosine triphosphate was then administered intravenously (0.14 mg/kg of body weight per minute) to record the spectral Doppler signal of the peak flow response induced by dilatation of the coronary microvessels. In the serial studies, we tried to record the spectral Doppler signal of LAD flow at the same portion of the artery in the same patient. All studies were acquired and stored digitally in the ultrasound system for off-line analysis. The ultrasound technicians were unaware of the patients' details. All patients had continuous heart rate and electrocardiographic monitoring. Systolic and diastolic blood pressure was recorded at baseline, at peak flow response, and at recovery. An experienced investigator who was blinded to the patients' status and data used the ultrasonography system computer to obtain off-line measurements. Mean diastolic coronary flow velocity (CFV) was measured by tracing the contour of the spectral Doppler signal at baseline and at peak flow response. An average of the measurements was obtained in 3 cardiac cycles. Coronary flow reserve was defined as the ratio of mean CFV at peak flow response to mean CFV at baseline.

Statistical analysis

All data are expressed as mean ± SD. The Wilcoxon signed-rank test was used to compare the 2 time points. The Mann-Whitney *U* test was performed to compare 2 groups of continuous variables. All tests were 2-tailed. The likelihood of a significant improvement in LVEF after therapy was assessed by logistic regression analysis. Spearman's rank correlation coefficients were calculated to study the associations between different variables. A value of $P < .05$ was accepted as statistically significant.

Table I. Characteristics of study population according to the change in LVEF at follow-up

	All patients (n = 18)	Group A (n = 10)	Group B (n = 8)	Group A vs Group B (*P*)
Age (y)	56 ± 15	54 ± 16	58 ± 15	NS
Women	6 (33)	3 (30)	3 (38)	NS
Dose (mg/d)	12 ± 6	13 ± 5	11 ± 8	NS
Follow-up (m)	12 ± 6	12 ± 5	12 ± 7	NS
Medications				
ACE/ARB	18 (100)	10 (100)	8 (100)	NS
Digitalis	3 (17)	1 (10)	2 (25)	NS
Diuretics	17 (94)	10 (100)	7 (88)	NS
Spironolactone	8 (44)	5 (50)	3 (38)	NS
Echocardiographic findings				
Baseline				
EDV (mL)	193 ± 42	196 ± 35	191 ± 60	NS
ESV (mL)	142 ± 44	144 ± 35	139 ± 54	NS
EF (%)	28 ± 7	27 ± 7	28 ± 7	NS
E/A	1.3 ± 0.9	1.3 ± 1.0	1.2 ± 1.0	NS
DT (ms)	179 ± 71	170 ± 62	189 ± 75	NS
1 m				
EDV (mL)	180 ± 46	181 ± 43	180 ± 52	NS
ESV (mL)	127 ± 42*	124 ± 40*	131 ± 47	NS
EF (%)	30 ± 8	31 ± 8*	29 ± 9	NS
E/A	0.9 ± 0.6	1.0 ± 0.7	0.9 ± 0.2	NS
DT (ms)	195 ± 56	195 ± 50	196 ± 53	NS
Follow-up				
EDV (mL)	139 ± 50*	122 ± 39*	162 ± 55*	<.05
ESV (mL)	88 ± 42*	70 ± 28*	112 ± 46	<.05
EF (%)	39 ± 9*	44 ± 6*	33 ± 8*	<.01
E/A	0.8 ± 0.2*	0.7 ± 0.3*	0.8 ± 0.2	NS
DT (ms)	206 ± 52*	206 ± 50	206 ± 60	NS

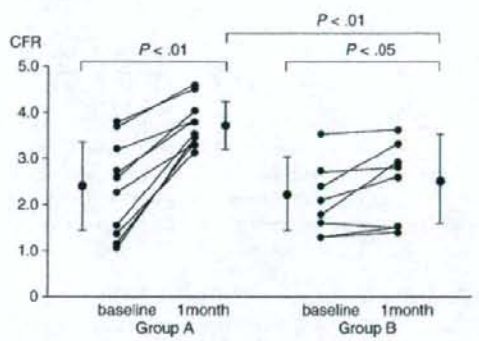
Data are presented as mean ± SD or number of patients (percentage of population). *ACE*, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin II receptor blocker; *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *EF*, ejection fraction; *DT*, E-wave deceleration time; *NS*, not significant.
* $P < .05$ vs baseline.

Table II. Coronary flow data at baseline and after 1 month of therapy

	All patients	Group A	Group B	Group A vs group B (*P*)
Baseline				
Resting CFV (cm/s)	24 ± 7	23 ± 6	25 ± 7	NS
Peak CFV (cm/s)	53 ± 21	53 ± 26	52 ± 15	NS
CFR	2.3 ± 0.9	2.4 ± 1.0	2.2 ± 0.8	NS
1 m				
Resting CFV (cm/s)	24 ± 6	22 ± 6	24 ± 8	NS
Peak CFV (cm/s)	70 ± 19*	78 ± 12*	61 ± 22	<.05
CFR	3.1 ± 0.9*	3.7 ± 0.5*	2.5 ± 0.9*	<.01
CFR change	0.9 ± 0.7	1.3 ± 0.6	0.4 ± 0.5	<.01

Values are mean ± SD.
* $P < .05$ vs baseline.

Figure 2



Individual change in CFR from baseline to 1 month of carvedilol therapy in the 2 groups.

Results

Characteristics of study population

Clinical and echocardiographic parameters at baseline, at 1 month, and at follow-up during carvedilol therapy divided into 2 groups are summarized in Table I. There was no significant difference between group A and group B in baseline characteristics such as age, sex, maintenance dose of carvedilol, follow-up period, other medications for heart failure, LV end-diastolic volume, end-systolic volume, LVEF, E/A, and E-wave deceleration time. After 1 month of carvedilol therapy, no difference was observed in echocardiographic findings between the 2 groups, although LV systolic volume and LVEF were slightly changed from baseline in group A. In the follow-up study, LV end-diastolic volume and end-systolic volume were smaller in group A than in group B (122 ± 39 vs 162 ± 55 mL, $P < .05$, and 70 ± 28 vs 112 ± 46 mL, $P < .05$, respectively). Left ventricular ejection fraction was higher in group A than in group B (44 ± 6% vs 33 ± 8%; $P < .01$).

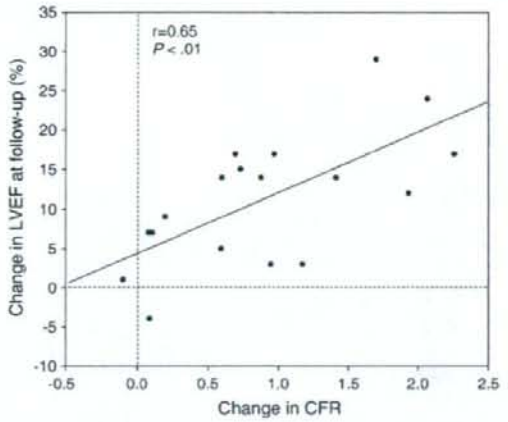
Hemodynamic data at baseline and at 1 month of therapy

There was no significant difference between group A and group B in mean blood pressure at baseline (95 ± 7 vs 95 ± 12 mm Hg; P = NS) and at 1 month of therapy (89 ± 6 vs 90 ± 18 mm Hg; P = NS), and in heart rate at baseline (84 ± 11 vs 80 ± 12 beats/min; P = NS) and at 1 month (65 ± 8 vs 68 ± 9 beats/min; P = NS).

Coronary flow data at baseline and at 1 month of therapy

Table II shows the coronary flow data at baseline and after 1 month of treatment with carvedilol. At baseline, there was no significant difference in resting CFV, peak CFV, and CFR between the 2 groups. At 1 month, however, peak CFV and CFR were significantly higher in group A than in group B (78 ± 12 vs 61 ± 22 cm/s, $P < .05$; 3.7 ± 0.5 vs 2.5 ± 0.9; $P < .01$), despite the lack of difference in resting CFV. Figure 2 shows the

Figure 3



Relation between change in LVEF on follow-up and that in CFR.

individual changes in CFR at baseline and after 1 month. After 1 month of therapy, CFR significantly increased from baseline in the both group ($P < .01$ in group A and $P < .05$ in group B). Change in CFR after 1 month of therapy was significantly greater in group A than in group B (1.3 ± 0.6 vs 0.4 ± 0.5; $P < .01$).

Coronary flow data and follow-up LVEF

Single logistic regression analysis revealed that CFR change ($P = .038$) predicted a significant improvement in LVEF at follow-up study, but the CFR at baseline ($P = .48$) and CFR at 1 month ($P = .075$) did not. Furthermore, a significant correlation was found between the change in CFR after 1 month and that in LVEF on follow-up ($r = 0.65$, $P < .01$) (Figure 3).

Discussion

To the best of our knowledge, the present follow-up study is the first to demonstrate the relationship between improvement in coronary circulation and subsequent recovery of LV function during β-blocker therapy in patients with IDC. The main findings of this study are as follows: (1) patients who have IDC with a significant improvement in LVEF at follow-up study have a greater improvement in CFR after short-term therapy; (2) early change in CFR have a potential predictive value for the response to therapy; and (3) the magnitude of early improvement in CFR shows a significant positive correlation with that of late improvement in LVEF. These observations suggest that improvement in coronary circulation after short-term therapy is associated with subsequent LV reverse remodeling during β-blocker therapy in patients with IDC.

In patients with IDC, CFR response to microvasodilators or to pacing tachycardia is impaired despite angiographically normal coronary arteries.[8-14] Impaired CFR in IDC is not only attributed to high extravascular pressure as the result of LV dysfunction,[11,13,14] but functional alterations of coronary microcirculation.[10] It has been reported that impairment of the hyperemic response of coronary blood flow in patients with IDC is independently associated with an increase in the risk of death and subsequent cardiac events.[25] These observations suggest that improving CFR in patients who have IDC with coronary microvascular dysfunction could influence prognosis positively.

β-Blocker therapy is a widely acceptable treatment strategy for heart failure in patients with LV systolic dysfunction.[7] In particular, carvedilol has been reported to be superior to other β-blockers.[4,5] It has a broad antiadrenergic activity blocking α_1-, β_1-, and β_2-adrenergic receptors. Furthermore, unlike other β-blockers, carvedilol has antioxidant and antiendothelin properties.[4,5] All these additional properties may contribute to the favorable outcome with carvedilol. We previously described that impaired CFR in patients with IDC is improved after a short-term administration of carvedilol and this improvement is observed before the improvement in LVEF.[16] Although the mechanisms of the increase in CFR after carvedilol therapy are not fully defined, it has been speculated that β-blocker may decrease coronary vascular resistance and improve coronary microcirculatory dysfunction, by the reduction in the extravascular compressive forces due to wall stress, or by dilation of coronary arteries in patients with IDC.[16,24,25] Furthermore, the α_1-adrenergic blocking action of carvedilol may induce additional vasodilation or alteration of the coronary microcirculation.[26] In addition to the previous data, the present study shows that improvement in CFR after short-term carvedilol therapy is associated with late recovery of LVEF. These data indicate that the improving CFR after carvedilol therapy might be one of the mechanisms by which carvedilol therapy has a favorable effect on LV function in patients with IDC, and that an increase in CFR may induce the late improvement in LV function. Skalidis et al[14] recently demonstrated a significant positive correlation between CFR and LV contractile reserve in patients with IDC, which is a predictor of further improvement in LVEF. In addition, they proposed a possible association between the restoration of CFR by any interventions such as β-blocker therapy and late improvement in LV function. Our follow-up data directly showed the relationship between CFR change after carvedilol therapy and subsequent recovery of LVEF as the result of response to carvedilol therapy.

From a clinical perspective, the improvement in coronary circulation could be a potential therapeutic goal in patients with IDC. In this study, we found a